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THE MANAGEMENT OF BLOOD PRESERVATION AND BLOOD SUBSTITUTES*, **, †

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THE enormous progress in the use of blood and its derivatives during the years of the war has been based in the main on two preëxisting bodies of knowledge, each in a different stage of development. The first comprises the elucidation over the previous decades by biological methods of the multiple functions of this fluid. With a few exceptions, the war effort has not added significantly to the known number of these functions, whether cellular or humoral. The second comprises the knowledge of the physical and chemical properties of the various substances and structures in which these functions reside.

The concerted application to blood of the methods and findings of a group of fundamental studies both in physics and in chemistry, undertaken in the prewar years frequently without reference to immediate

* An address delivered at the Eighteenth Graduate Fortnight of The New York Academy of Medicine on the "Contributions of the War Effort to Medicine."

** The bibliography has been selected quite arbitrarily from the very extensive literature such that a more detailed acquaintance with subdivisions of the field may be acquired from the bibliographies of the individual articles cited.

† Much of the work reviewed has been carried out under contracts between various laboratories throughout the country and the Office of Scientific Research and Development. Specific acknowledgments of these contracts are given in the publications of the individual laboratories.

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utility, has permitted within a remarkably short time the unprecedented extension of the therapeutic range of several of the functions already known.

Therefore, in considering the contribution of the war effort to medicine in the field of blood, I would like to take up with you certain of the techniques used to separate, concentrate and stabilize these functions in the preparations which have been made available to the armed forces in quantities hitherto unattained in military medicine, the range of efficacy of these preparations in conditions varying between shock and virus infections, and the type of property on the basis of which substitutes for blood functions have been appraised.*

Whole Blood and Red Cells**

The necessity for the respiratory function of hemoglobin in the field treatment of many forms of casualty was well recognized early in the war.[2] Many investigations[3,4] on the intravenous administration of preparations of purified hemoglobin have not as yet yielded a completely satisfactory substitute for the function of this pigment in its natural state in the erythrocyte.

The transportation, storage and use of erythrocytes in war medicine demand a knowledge of the effect of field conditions on their physical stability. Before 1940 there existed essentially two techniques for evaluation of red cell stability. For the first of these, namely fragility in hypotonic salt solutions, correlation was inadequate with survival time in the body following transfusion. The sole method of measuring the latter property (which is critical in the determination of safety and utility of transfusion) lay in the method of differential agglutination.[5,6] This consisted of the transfusion of type O cells into type A or type B donors and the estimation of the proportion of surviving cells at subsequent times by agglutinating the cells of the recipient with anti-A or anti-B isoagglutinin.

The development within the last three years of radioactive iron techniques has provided a far more accurate measurement of *in vivo* red cell survival.

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* The role of the Subcommittee on Blood Substitutes of the National Research Council both in appraisal and in recommendation directly to the armed forces, together with the varied qualifications of the experts who served as members and consultants, have been described by one of its members in another place.[1]

**In preparing this section, the writer gratefully acknowledges the assistance of Dr. J. G. Gibson, II, and Dr. J. F. Ross.

The original studies of Hahn and his colleagues[7] in animals and of Ross and Chapin[8] in humans employed a mixture of radioactive isotopes of iron, prepared by bombardment in the cyclotron of iron phosphide. Subsequently, Evans and his co-workers,[9] at the Radioactivity Center of the Massachusetts Institute of Technology, have developed methods for preparing two separate isotopes by bombardment of manganese and cobalt respectively. The half-life of one of these isotopes is five years; that of the other, forty-seven days. The fact that the first has its principal radiation in the form of x-rays and the second in the form of beta rays (energetic electrons) has been utilized in constructing a Geiger counting chamber with windows specifically sensitive to the radiation of each isotope.

With each isotope there have been developed three products safe for human injection: (1) radioactive iron in the form of ferric ammonium citrate, (2) radioactive hemoglobin derived from the cells of patients who have received radioactive iron, and (3) their red cells containing radioactive hemoglobin.

Despite much earlier work (beginning in 1916 with the addition of glucose to citrated whole blood by Rous and Turner[10]), Ross[11] stated, in 1944, that preservation had "not as yet been developed sufficiently to allow shipment of blood to the battlefronts," nor had the conditions of refrigeration and mechanical trauma most conducive to *in vivo* survival of red cells been established. Several groups, working in collaboration with the staff of the Radioactivity Center of the Massachusetts Institute of Technology, have in the interim by means of radioactive cells[12] studied these conditions with sufficient accuracy to permit the definite establishment of such facts as these—that whole blood should be taken into a chilled acidified citrate solution, and that it should be maintained without deviation from refrigerating temperature from that time until when it is used. Through comparative studies of chemical conditions of preservation, there has been achieved a preservative solution permitting 70 per cent 24-hour *in vivo* survival of red cells following storage for over 20 days. Stabilities of this order led to the airplane delivery from the United States to a Pacific battle-front of whole blood in units greater than half a million, dropped by parachute in expendable refrigerators, in one of the later Pacific campaigns without any reports, despite careful investigation, of severe hemolytic transfusion reactions.

The specifications of the particular preservative used probably do

not represent the upper limit of red cell stability which may emerge from further systematic study of the properties of the red cell structure. For indeed, the substances that have been used in red cell preservation have thus far been chosen to some extent on an empirical basis, and owing to the necessity of the rapid attainment of a practical solution to the problem imposed by the war, systematic investigations of the mechanism of action have been postponed.

Economic considerations arising from the fact that the number of clinical conditions requiring therapy by plasma or its fractions exceed those requiring red cells make it highly desirable in military as well as in large-scale civilian medicine to utilize red cells independent of plasma. Whereas sufficient to admit of use in base or civilian hospitals, the *in vivo* posttransfusion stability achieved in separated washed red cells has not yet been comparable to that of red cells stored in the presence of plasma. Thus, field use of washed cells in significant quantities did not occur in this war.

Cells from which plasma has been removed without either washing or addition of other agents show higher stability than washed cells, indeed, high enough to make this procedure of current value in blood banks.

The apparent stabilizing activity of plasma leads to the suspicion that there may be a separable substance in which this property might be concentrated. This possibility has been investigated by Hughes and his collaborators.[13]

The new products containing radioactive iron are being turned to peacetime use in further studies of iron metabolism. They make possible the definition of rates of red cell formation and destruction in the elucidation of the mechanisms of anemias with considerable accuracy, particularly in that differentiation between the two isotopes permits the quantitative study of segments of the cell population of two known ages.[14,15]

Plasma, Liquid, Frozen, and Dried

In contrast to the state of knowledge on the preservation of red cells at the start of the European war, the state of knowledge of the therapeutic efficacy of whole plasma stored either liquid or frozen was sufficiently advanced to permit limited military use well before the entry of the United States. As early as 1941, Scudder and his co-workers of

the Blood Transfusion Association,[16] in collaboration with the American Red Cross and several New York hospitals, collected and shipped to England liquid plasma in an amount which for that time was quite considerable. The initial incidence of bacterial contaminations encountered in the early large-scale operations has been sufficiently reduced by such measures as a closed system of preparation with meticulous aseptic technique that, in 1944, Lezner and Newhouser, in analyzing the results of over 1,700 administrations in Naval medical activities on this continent,[17] concluded that it is safe to preserve plasma in the liquid state at room temperature in moderate climates for periods up to at least two years.

The temperature occasionally obtaining both in ships and tanks set a limit to the field utility of liquid plasma. A chemical step significantly increasing temperature stability is McFarlane's[18] lipoid extraction by freezing at approximately -20°C. in the presence of ether, followed by ether removal. Though of value in Great Britain[19] by reason of scarcity of drying equipment, this never was widely used in this country, in part because of the high stabilities attained for field use by drying plasma *in vacuo* from the frozen state. This method was found by Flosdorf and Mudd,[20] in 1935, to produce comparatively little alteration in physical and chemical properties of certain types of proteins. Its adaptation to industrial use, pioneered by such workers as Strumia,[21] and the definition of the conditions of drying and bottling yielding both high stability and short resolution times made possible the preparation of enormous quantities of this convenient, readily soluble, yellow powder from blood collected by the American Red Cross Donor Services throughout the nation.[22] The unit in general use at the end of the war, consisting of the dried solids from approximately 500 cc. of plasma, packaged with intravenous equipment and sterile distilled water for resolution, was admirably adapted to field use where the bulk of the package was no disadvantage. The general availability of this product undoubtedly proved to be one of the great lifesaving measures in many campaigns of the war.

The incidence of homologous serum jaundice (whose magnitude is not yet defined in the several series available for study) may well increase with increasing size of plasma pools. Transmission is not obviated by drying.[23] The risk of this disease, whose course is not always benign,[24] will undoubtedly influence the peacetime management of collection

and pooling of plasma and, indeed, the indications for its use should satisfactory materials freed of this risk become generally available.

The property which gives whole plasma its chief value in acute emergencies of military surgery is the capacity of the proteins to hold fluid within the blood stream by reason of both size and high net charge.[25] Plasma albumin, comprising only about one-half of the plasma proteins by weight,[26] contributes four-fifths of the power of plasma to perform this function. The other protein components, containing specific substances carrying many other functions and capable of widely divergent therapeutic adaptations, possess this power to a much lesser degree. The program of plasma fractionation has had as its aim during the war the large-scale separation, purification, concentration, and stabilization of those components which might prove of value in military medicine, and their distribution for appraisal and use in forms best suited to clinical needs.

Methods and Products of Plasma Fractionation

To avoid prolonged dialyses (necessary for salt removal in methods based on differences of protein solubility in concentrated salt solution[27]), Cohn and his collaborators [28,29] introduced into large-scale fractionation organic solvents removable by volatilization at low temperature and pressure. The low temperature use of organic solvents, although hitherto a systematically unexplored field in protein preparation, had been previously studied here and abroad. In 1910, Hardy and Gardiner[30] had employed alcohol-ether mixtures at very low temperatures to precipitate the plasma proteins and remove associated lipoids. Alcohol precipitation was one of the steps employed in Felton's procedure for concentration of antipneumococcus antibodies from horse serum in 1926.[31] Later, Ferry and his co-workers[32] showed that egg albumin maintained at low temperatures in ethanol-water mixtures could still be crystallized.

With increasing experience in carrying out separations, it became apparent that the use of organic solvents at low temperatures had a second advantage beyond easy removability, namely, that in their presence the solubility of plasma proteins could be so reduced at low salt concentrations that specific electrical interactions, usually masked at higher salt concentrations, could bring about more selective precipitations than possible where the salt itself is used as a precipitant and the solubility behavior of various proteins of differing biological function is more nearly alike.

Predicated on the assumption that protein molecules of different biological function will to some degree possess different structure, standardization of the various fractions was carried out by means of a variety of physical tools designed (in the main before the war) in laboratories both here and abroad with a view toward the precise measurement of physical and chemical constants of large molecules in terms of which their behavior might be interpreted. Two instruments have been particularly useful. The first is the ultracentrifuge of Svedberg,[33] which classifies large molecules according to their speed of motion in a gravitational field and which in combination with measurements of diffusion or viscosity properties of proteins yields information as to size and shape. The second is the electrophoresis apparatus of Tiselius,[34] which has yielded a classification of the plasma proteins according to their speed of motion in an electrical field, a property which although extraordinarily useful from an empirical point of view is theoretically difficult of precise interpretation.[35] In many instances, methods of measurement now available are not sufficiently sensitive to yield differences in fine structure between molecules of apparently identical size, shape and electrical properties though of divergent functions.

The extension of fractionation from a laboratory glassware stage to an industrial scale, in which the plasma of over two million donors approximating in volume some 120,000 gallons was fractionated, was carried out through the construction of a pilot plant at the Harvard Medical School. To this came chemists from the commercial laboratories for study in collaboration with the pilot plant group of the processes and equipment which were later adopted in setting up the commercial plants. The continuing collaboration between these groups, involving many visits between the staffs of both pilot and commercial plants, was in great measure responsible for the successful use of the fractionation methods as they were developed and modified throughout the war.

The adaptation of the chemical specifications of various products to clinical needs has in turn involved collaboration between the clinical groups responsible for appraisal and the chemical groups responsible for production. In those areas where continuity and closeness in this collaboration have been sufficient to give the clinicians some grasp of the range of chemical properties attainable and the chemists some notion of the nature of clinical phenomena and of the applicability and limitations of quantitive methods in their study, progress toward clinical use

has been usually rapid.*

The results of the fractionation program have been twofold. The first has been the separation and concentration in usable form of the osmotic, the isoagglutinin, certain of the immune, and certain of the coagulation functions of blood. The properties of these products and their uses developed to date have been the subject of many papers ranging from the earlier studies of Janeway and his co-workers[36] on the use of human serum albumin in experimental human blood loss to the studies now in progress on the use of the antihemophilic function of the blood;[37] certain of the more recently studied uses of gamma globulin in prevention of hepatitis[38] and of salt-poor albumin in the treatment of edema of hepatic and renal origin[39,40] have been discussed in this series of addresses by Dr. Stokes and Dr. Thorn. Further detail on flexibility of properties and uses will not be presented here. The separations that have been made are not uniformly sharp; the aim has of necessity been a combination of sufficient purity necessary for use together with maximum yield. Thus, for example, whereas normal human serum albumin is electrophoretically homogeneous, prothrombin as currently prepared is not so, and the antihemophilic substance[41] has not yet been separated from fibrinogen under conditions which leave each in a usable form.

The second result is to provide in a small number of standardized fractions of plasma and their various subfractions, reagents, or starting materials for preparation of reagents, sufficiently pure such that the mechanism of their chemical interactions may be more accurately studied and the conditions governing their equilibrium in the body defined. The currently standard fractions and subfractions are by no means final. Quite a different system of conditions may be necessary to concentrate certain other substances not as yet purified.

Blood Substitutes

For each of the various functions of human plasma which have been thus separated and concentrated, there usually exist in the comparable tissue of animals substances with similar functions which under restricted circumstances may be made applicable to use in human therapy.

* Acknowledgment of the large groups of collaborators, both chemical and clinical, will be found in the many recent reviews of Cohn, who directed the development of the plasma fractionation program, and in two series of articles, entitled "Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation." and "Preparation and Properties of Serum and Plasma Proteins," appearing in the *Journal of Clinical Investigation*, and the *Journal of the American Chemical Society*, respectively.

All proteins of other than human origin are potential antigens. Thus, in the evaluation of any product of heterologous origin to replace the parallel human product in therapy, it must be shown that the danger of reactions based on an immunological mechanism has by reason either of purification, chemical modification, or site of use been obviated.

About the time Wangensteen published the first of his extended studies on the injection of bovine plasma in man,[42] at the suggestion of the late Dr. Walter B. Cannon a systematic study of certain purified animal proteins was initiated. Moreover, in many laboratories various forms of physical and chemical treatment have been used in attempts to modify the antigenicity of foreign proteins without excessive alteration in physical-chemical properties or biological function.

Despite such encouraging early findings as wide variation in antigenicity between several components of plasma of a given species,[43] during the period of the war no products emerging from this work were used in military medicine.* For this, antigenicity has not been the sole responsible factor.

The evaluation of a substitute for the natural substance performing a given function must be made not only in terms of the adequate capacity to perform the function but also in terms of the other properties, advantageous or disadvantageous, of the substitute substituent material of which antigenicity is only one.

For instance, a substance designed to increase plasma colloid osmotic pressure must be considered with respect to the distribution of molecular sizes and shapes (which will in part determine duration of efficacy); with respect to effect on blood viscosity (due either to intrinsic molecular asymmetry or effect on red cell aggregation); with respect to effect on equilibrium of the various plasma proteins with the tissues, and on the capacity for their regeneration; with respect to distribution and effect on tissues themselves (particularly with reference to "storage diseases"); with respect to nutritional capacity; and ultimately (as in the case of all "blood substitutes") with respect to cost and feasibility of standardized safe production.

Such properties determine the therapeutic scope of a material. Thus, the gelatins, a group of degradation products of animal collagen, have long been known to lack antigenicity.[44] The immediate increases in plasma volume following injection of either human albumin or certain

* Indeed, no products of other than human origin were recommended to the armed forces by the Subcommittee on Blood Substitutes of the Natonal Research Council.[1]

gelatins[45,46] make these substances comparable in the short-term treatment of shock in the previously healthy patient. Rapid urinary loss (in part by reason of small molecular diameter[47]), together with poorness in certain essential amino acids, makes gelatin far less valuable than albumin in treatment of the problems consequent upon the hypoproteinemia seen in surgical and medical practice.

For products whose route is not intravenous, obviously other groups of properties take prominence in evaluation. Thus, for those which have contact with brain tissue the relation between those physical and chemical properties susceptible of standardization and sequences of tissue response are highly important; antigenicity may prove less so. Indeed, the accumulating surgical experience with bovine thrombin (under certain circumstances highly antigenic[48]) has as yet suggested very little risk attached to its repeated application in the same patient. Its hemostatic use[49] in conjunction with an absorbable matrix, soluble cellulose,[50] is discussed by Dr. Frantz elsewhere in this series of addresses.[51]

There is no question that an increasing group of satisfactory substitutes for blood functions will be of great value not only in the practice of medicine by reason of convenience and economy, but in the development of further therapeutic advances by releasing human material to new investigations.

It is worth pointing out advantages apparently inherent in having systematic study of natural functional substances in a tissue proceed simultaneously with, if not precede, study of "substitutes," either heterologous or synthetic. This pattern of investigation (achieved spontaneously in such fields as endocrinology) has proved peculiarly profitable in the field of blood. It has resulted in the availability of methods for preparation in quantity of many natural materials which, although apparently merely by-products in wartime, may have considerable significance for peacetime therapy. Had the wartime research activity been limited solely to the empirical search for economical substitutes for those therapeutic possibilities of blood most obvious at the start of the war, it is possible that many developments of significance in military surgery (for example, dural substitutes developed from human fibrinogen and thrombin) would have been postponed.

Peacetime Blood Management

In that there is no substitute for the human erythrocyte, human

blood must still be collected. The initiation of plans of central collection in connection with state programs of plasma fractionation gives evidence that the Red Cross wartime experience in this field will find continued application.

In the management and distribution of centrally collected blood, group O red cells,* of known Rh typing and resuspended in a medium yielding satisfactory *in vivo* stability, may prove an excellent standard preparation for large metropolitan hospitals and, indeed, could be shipped to small outlying hospitals for which the maintenance and staffing of the type of blood bank used in metropolitan hospitals is unduly expensive. There will doubtless be sufficient red cells of other types to cover experimental needs in those areas where study of components and functions of erythrocytes is active.

The effect of the shift of emphasis from military to civil medicine on the demand for the various products which have already been standardized in plasma fractionation can not now be predicted with accuracy, chiefly because in many instances the range of clinical applicability is not yet fully explored. For example, attenuation in measles and passive immunization in hepatitis can probably consume as much concentrated antibody-containing gamma globulin from normal subjects as can be supplied; the effect of early massive doses of normal gamma globulin in the prevention of relapse or fatal progression seen in a certain proportion of hepatitis patients is not certain. The effect of enzymatic hydrolysis on cellular penetration of antibody in those diseases where the infectious agent is chiefly intracellular (e.g., rickettsial) has not been thoroughly studied. The preventive and therapeutic possibilities of similarly concentrated gamma globulin of hyperimmune subjects (convalescent from various diseases) are not yet worked out.

Moreover, there are in plasma many substances of possible clinical value which are yet relatively unexplored from the chemical standpoint. Among them are cholinesterase which, if sufficiently concentrated in a preparation suitable for parenteral use, might be of interest in connection with conditions not readily subject to surgical parasympathectomy (e.g., ulcerative colitis); the plasma fibrinolytic enzyme which, if sufficiently purified, might prove free of dangers attending use of current preparations and be suitable for study in subacute bacterial endocardi-

* The recent observations of Emerson and his colleagues[52] on hemolysis of recipient cells following transfusion of group O whole blood emphasize the necessity of the removal of isoagglutinins either by chemical means or by separation of the plasma.

tis resistant to the combination of chemotherapy and anticoagulants.

It is now as impossible to predict where in this group of substances clinical success will be achieved as it would have been to predict the prophylactic success attained in hepatitis with concentrated gamma globulin at the start of the plasma fractionation program.

The task of finding appropriate conditions for the separation and purification of substances yet unstudied will fall increasingly on the investigative chemists associated with state and other laboratories engaged in blood processing. There is no assurance that the laboratories which have assumed during wartime a responsibility, often nationwide and controlling, for collaboration between chemical research, production units, and clinical units will continue to carry this responsibility in peacetime beyond an advisory level. Moreover, the value of continuation may well be questioned from the standpoint of the individual scientists involved and the ultimate progress of the fundamental sciences. The extremely rapid development facilitated by the wartime centralized collaboration is to a great extent based on the implications of two decades of investigation, both in the fundamental sciences and the clinic, without such centralization.

As the pressure for immediate utility diminishes and many chemists and physicists turn to the advancement of their own fields, the advances in clinical use of blood will become slower. They are most likely to occur where clinicians, interested in a given group of diseases, have sufficient familiarity with chemical developments to see and assist the chemists to see the potentialities and to utilize the chemists' wisdom in adaptation of products to experimental and clinical requirements and in the control of chemical uniformity; that is to say, in those areas where the clinic is able to assume the principal responsibility for the pattern of collaboration which in the war has proved fruitful under greater centralization.

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PLANNED CONVALESCENCE*

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DURING the past four years Medicine accepted the challenge of total war and has made great advances which will be a boon to mankind in time of peace. Although they were the most widely publicized, these advances were not limited to science and technology, but were also in the field of human relationship; the bond between the patient and the doctor has had a rebirth. Thousands of doctors and millions of men are returning to their communities with closer bonds than ever before as a result of war experience. The science and art of medicine have become welded inextricably to meet the physical and spiritual needs of man.

This has been particularly true in the field of rehabilitation and convalescent care, where a close patient-doctor relationship became the keystone of the treatment and management of casualties returning from combat theatres. Early in the war when the conservation of manpower made necessary a comprehensive program, in order to reclaim every man possible for the military service, the Army Air Forces formulated a program based on this concept.

In those dark and uncertain days, every man-hour of training was unbelievably important. Flying schools, radio schools and mechanic's schools worked around the clock, twenty-four hours a day, seven days a week. It was necessary for every man to pull his share of the load. Yet, in our military hospitals thousands of men who had completed their definitive medical care sat around waiting for time to complete their convalescence. The hours they spent in boredom without purposeful activity did not contribute to the mission of the Army Air Forces.

THE AAF CONVALESCENT TRAINING PROGRAM

It was in an effort to provide for the purposeful employment of

* Pesented October 9, 1945 in the 18th Graduate Fortnight of The New York Academy of Medicine.

this hitherto wasted time, and to utilize a program of activity as an adjunct to the definitive medical care of the sick soldier, that the Convalescent Training Program was established in all AAF hospitals in December, 1942. The purpose of that program was two fold: first, to send the soldier back to duty in the best possible physical condition in the shortest possible time; second, to teach the soldier-patient something that would make him a more efficient and effective fighting man.

Physical reconditioning was accomplished by a systematic, graduated series of calisthenics and corrective exercises. Given at first in their mildest form even to bed patients, the exertion was gradually increased in ratio to the patient's physical tolerance until before returning to duty, he was able to participate in a comprehensive program of drill, hikes, calisthenics, athletics and fatigue duties. Exercises were begun in bed as soon as the patient's condition permitted, to prevent muscular atrophy in the unaffected parts and general deconditioning phenomena. Pneumonia patients were given deep breathing, hand, arm and chest exercises as soon as their temperature returned to normal. Physical activity was as much a part of the doctor's prescription as drugs and diet.

Minds were not permitted to become stagnant. Time formerly wasted in reading comic books and mystery stories was spent purposefully. The classroom was moved into the wards and training films, chemical warfare classes, radio code practice periods, and discussions on "Why We Fight" and "The Postwar World" became an integral part of the hospital day. Radios, carburetors and even airplane engines were brought into the wards and sun rooms. The hospital was transformed into a combination gymnasium, schoolroom, machine shop and New England Town Hall. This program has been made a permanent part of the postwar military medical service.

Physical Reconditioning

Early in the convalescent program it was noted that, to obtain maximum results, reconditioning had to start at the earliest possible moment following acute disease or injury. It had to be purposeful, progressive, and graduated as the patient's physical tolerance increased. Special corrective exercises had to be designed to meet specific military needs and experienced physical training instructors were given special instruction on administering them. A positive attempt was made to correlate ward fatigue and detail work with the soldier's disability to

aid in functional recovery. Men with hand, finger and wrist injuries were given fatigue duties that involved finger and hand manipulation. Those with bad backs or knees were given duties which involved bending, stretching, kneeling, lifting, and other movements which aided in strengthening the affected part.

The *Handbook of Recovery*[1] (AF Manual No. 23) was prepared as a prescription blank for all types of orthopedic disabilities. It included a nine-page section on anatomy, physiology and pathology written in simple language to show the soldier-patient why he was in the program, the value and effects of active exercise, how bones, muscles and nerves are made, what happens when they are injured and how they heal. This was followed by a series of two-page prescription blanks for the specific injury, demonstrating to the soldier-patient by diagram the normal function of the injured part, his diagnosis and disability, the type of physiotherapy prescribed, the illustrated active exercises to be done with and without supervision, and a personal objective recovery chart which the patient kept himself. This was an effective innovation as it not only gave the patient an insight into and understanding of his condition, but great motivation through his ability to measure his own progress objectively. An accompanying instructor's manual *Handbook of Physical Retraining*[2] (AF Manual No. 24) was prepared for the guidance and use of the physical reconditioning instructors in order that they might properly administer and supervise the exercises to obtain maximum results.

Let's Walk[3] (AF Manual No. 49) was another publication designed for the patient which met with widespread use and approval. Unique in its presentation, this booklet dealt with the functional aspects of walking with the use of aids. It first gave the patient a brief, psychological orientation to his disability and then proceeded to demonstrate objectively, through the use of illustration and charts, the factors involved in walking with aids, the muscles which must be utilized and therefore strengthened to use walking aids effectively, the techniques and gaits of walking, practical hints on care of the aids, and most important, insight and motivation.

Results of the Program

More interesting, however, and equally as significant as the means used to meet the objectives, were the ends themselves. Some of the

pertinent observations of the Convalescent Training Program after nearly three years of experience were: hospitalization time was shortened; hospital readmissions were reduced; sick leaves were eliminated except in extraordinary cases; and the morale of the soldier-patients was immeasurably improved when they were kept busy and interested in purposeful activity.

A number of interesting clinical studies were made. Van Ravenswaay and his co-workers[4] studied 645 cases of virus pneumonia, all treated in the same acute wards. They were then assigned to alternate convalescent wards. In Ward I "nature was allowed to take its course" and the men sat around and waited until they and the medical officer felt they were ready for duty. In Ward II the patients were kept in bed until their sedimentation rate reached 10 mm. in one-half hour and then were put in a reconditioning program, beginning with exercise for one-half hour the first day, and increasing progressively until the twelfth day when the patients were participating in a full six-hour day of physical training, mass games, competitive sports and active recreation including a ten mile hike. Group I averaged 45 days hospitalization with a 30 per cent recurrence rate; Group II, at the end of 31 days, was discharged to duty with but a 3 per cent recurrence rate; 45 days hospitalization, unsupervised; 31 days with graduated conditioning—a 30 per cent recurrence rate in the unsupervised compared with but a 3 per cent recurrence rate in the supervised.

Karpovich and his associates[5] at the School of Aviation Medicine, San Antonio, Texas, studied a similar group of 200 aviation cadets convalescing from virus pneumonia. Using a modification of the Harvard Step Test and starting as early as the first afebrile day, Karpovich found that by the reactions to this test it was possible to determine, with some degree of accuracy, the patient's ability to enter into, and participate in, an active convalescent program. An interesting by-product of Karpovich's observations was that patients being tested required five days less hospitalization time than those participating in the general program—pointing out the tolerance and ability of these men to participate in an even more active program with beneficial results.

Marquardt,[6] at the AAF Regional Station Hospital No. 1, Coral Gables, Florida, made an interesting observation on a small group of patients recovering from virus pneumonia. These patients were clinically well but had residual persistently positive x-ray findings. They were

put on hyperventilation every waking hour, twelve times a day, and serial x-rays were made every twelve hours. Over 90 per cent of the patients in the series became x-ray clear in a period of 96 hours.

As a part of the AAF Rheumatic Fever Control Program, Karpovich, Weiss, Starr and Ershler[7] did a study on physical fitness testing and physical training of convalescent rheumatic fever patients. Because of the chronic, recurrent nature of the disease and the possibility of disabling cardiac sequelae, it was felt that special emphasis should be placed on the standardization of physical activity and convalescent training for these patients. This was achieved by working out a series of graduated physical fitness tests which could be used in conjunction with the usual clinical observation to determine the rate by which the patient could safely be permitted to progress to increased physical activity.

Using a modification of the Harvard Step Test with two benches 12 and 20 inches in height, and a cadence of twenty-four steps per minute, physical testing was started when, in the judgment of the medical officer, the patient should be permitted to be out of bed in a chair. The first test involved twelve step-ups in thirty seconds, using the 12 inch stool. Criteria for passing that test were a pulse rate less than 100 per minute one minute after the exercise, and good coördination in performance. If the patient passed this test and the medical officer concurred, he was allowed to be ambulatory in the ward. Using the same criteria, the next test involved twelve step-ups in thirty seconds using the 20-inch stool. In this test it was found that body metabolism in the average individual was raised eight to ten times. If the patient passed this test, he was placed on a program of graduated ward calisthenics. These exercises were given ten minutes twice daily to start, and continued over a period of approximately three weeks; they were then increased to thirty minutes twice daily. The exercises used at the beginning of this program were found to raise body metabolism roughly three times. The degree of strenuousness of the exercises during this period was gradually increased to a level which raised the metabolic rate seven to nine times the normal.

The next level of physical fitness testing was designated the progressive test, consisting of twenty-four step-ups per minute to a 20 inch bench for a period of five minutes. Scoring was based on the duration of the exercise plus the pulse rate one minute after exercise. If the patient made a minimal passing score on this test and the medical officer in

charge concurred, he was placed in the barracks phase of the program with a minimum stay of two weeks in each of the four periods. In the first period, physical training was given for forty minutes daily; in the second period, fifty minutes daily; in the third, seventy minutes daily; and in the final period, ninety minutes daily. Intensity of exercise was increased in each period and progressions were made only with the concurrence of the medical officer in charge. Progressions from period one to period two were automatic after two weeks, but progression from period two to period three was dependent upon the score made on the progressive test. There were no recurrences or untoward reactions in the patients used in the study.

It is interesting to note that before a comprehensive rehabilitation program was inaugurated in the hospital, approximately 85 per cent of patients with rheumatic fever were discharged from the service on medical grounds. After the inauguration of the program, augmented by special vocational and educational training classes and selective placement, 85 per cent of the rheumatic fever patients were retained in the service, and those returning to civilian life were oriented as to their vocational possibilities and limitations.

The standard AAF Physical Fitness Test, consisting of chin-ups, sit-ups, and running against time, was administered to five thousand patients of all types on their day of discharge from the hospital. These men made approximately 30 per cent better scores than the average made by troops on duty status at the same bases, which conclusively indicated that men leaving the hospital were physically fit for duty.

In addition to the physical reconditioning program, the men in the Convalescent Training Program were given educational training based on their individual needs. General instruction in military subjects was given to all men, with individual instruction in such subjects as mathematics, weather, navigation, blue print reading, radio, mechanics, and other specialties designed to increase his military effectiveness or aid in his return to civilian life.

The Convalescent Hospital

When overseas combat patients started entering the hospitals in 1943, it was realized that the training program carried on for the pre-combat trainee as outlined above, did not meet their total needs. For this reason special convalescent hospitals were activated to provide planned con-

valescence and rehabilitation following the completion of definitive care. These hospitals were designed to meet the needs of the whole man, regardless of what those needs were—medical, physical, psychiatric, social, vocational, educational or personal. The physical reconditioning program emphasized competitive team play and active recreation including athletics, bicycling, horseback riding, fishing, swimming, hiking and skiing.

The educational program consisted of training in military specialties, academic courses, commercial education, general and specialized woodworking, metal working and machine shop practice, welding, photography, electrical and radio repair, and numerous other courses. Diversified activities such as journalism, radio broadcasting, dramatics, art, handicrafts and other avocational activities, were more than diversional in that they provided the media, along with personal counseling and a well-rounded recreation program, for psychological readjustment and resocialization.

The purpose of the program was to provide the soldier-patient with a laboratory of opportunity through physical reconditioning, educational-avocational pursuits, and recreation, where he might recover the attitudes, habits and values compatible with normal behavior patterns.

In the convalescent hospital each patient was assigned to a designated physician who became his "family doctor" for the period of his hospitalization. This personal physician was the captain of the team of medical specialists, physical therapists, educators, athletic trainers, occupational therapists, social service workers, personal counselors and vocational guidance experts, and as such, integrated their efforts in the treatment of the whole man.

For the men who were being separated from the service on the basis of disability, there was, in addition to physical reconditioning, educational training, psychological adjustment and resocialization opportunities, a complete program of vocational guidance based on achievement, aptitude and functional testing, and interests determined by a series of short work experiences. In these short work experiences under a staff of trained vocational instructors, the patient had an opportunity to participate in a diversified educational program. He learned not only what he liked to do but what he was able to do, both in terms of ability and in terms of any handicaps he had. He knew at the end of this period what he enjoyed doing, what he was able to do, and the

occupations for which he possessed aptitudes. This information was then correlated by a skilled vocational counselor with the job opportunities in the field chosen, and the patient upon discharge from the hospital, had a complete objective vocational profile of himself, and insight into his specific problem.

The experience gained in rehabilitation and convalescent care in military medicine presents new opportunities in civilian practice. Today public attention is focused on the thousands of veterans who are returning from the war, handicapped and disabled. Yet few of us stop to realize that rehabilitation is not primarily a military problem. Prior to the onset of World War II the United States Public Health Service has estimated that there were some 23,000,000 persons in this nation who were handicapped by disease, accident, and maladjustment from former wars, to the extent of needing rehabilitation or selective placement in order to become fully employable. Accidents alone give us some 350,000 permanently disabled each year.[8]

During the first four years of war there were approximately 17,000 amputations in the Army, but during this same period there were more than 120,000 major amputations from disease and accident in our civilian population. We had in 1940 some six and one-half million disabled males between the ages of 15 and 64 years, men who normally would be income-producing. The armed forces and some outstanding community and civilian agencies such as New York's famed Institute for the Crippled and Disabled have demonstrated that the physical and emotional rehabilitation of this large segment of our population is possible. The Institute's staff with their twenty-five years' experience estimate that up to 97 per cent of all our handicapped can be rehabilitated to such an extent that they can be gainfully employed.

The Office of Vocational Rehabilitation, operating under the Federal Security Agency, has shown that rehabilitation pays off economically. Of the 43,997 persons undergoing vocational rehabilitation under the federal-state programs of this agency in 1944, 22 per cent, or more than 10,000, had never been gainfully employed, and nearly 90 per cent were not employed at the time they started their rehabilitation. The average annual wage of the entire group prior to rehabilitation was $148. After rehabilitation, the average annual wage of the group increased to $1,768. The total earnings of the entire group rose from $6,510,556 to $77,786,696.[9]

Prior to rehabilitation the majority of these persons relied on general public assistance, not only for the disabled individual but also for his family. The annual cost of this assistance to the taxpayer was from $300 to $500 per case, but the total cost of their rehabilitation, a non-recurring expense, averaged only $300 per case.

The short labor market during the war gave many of our disabled persons the first opportunity of their lives to take a place on the production line and prove that they could, with selective placement, produce on par with the normal worker. An example is the Ford Motor Company River Rouge plant, where more than 11,000 handicapped civilian workers were employed.

During the war 83 per cent of our nation's industries employed handicapped workers. Those industries have reported that among the handicapped there was a much smaller labor turnover, less absenteeism, fewer accidents and equal or higher production rates. Many employers, before this vast experience with the handicapped, had a fear of increased accident rates. The industrial accident rate of 87 of the great industrial plants in America, each having from 50 to 12,000 handicapped employees, has proved this a misconception. Their reports show that 56 per cent found the accident rate of the handicapped lower than that of the able-bodied; 42 per cent found the rate the same as for the able-bodied; and only 2 per cent found it to be higher.

A statement of policy of the Association of Casualty and Surety Executives, composed of sixty-five major insurance and surety companies, states explicitly that no higher rate for workmen's compensation is charged because of the employment of handicapped workers.

A survey of a number of Westinghouse Electric Company plants disclosed that approximately 10 per cent of the occupations could be performed satisfactorily by persons having one leg, 17 per cent by operators who had to use crutches, 82 per cent by men with only one eye, and 82 per cent by the deaf. Although much work still needs to be done in analyzing the physical requirements of the job and the physical capacities of the worker in objective terms, the United States Employment Service has developed adequate tools and techniques to meet the needs of the bulk of our handicapped population.

The answer to the utilization of handicapped workers lies not so much in "fitting the job to the worker" as in "fitting the worker to the job." Through this procedure the worker in reality becomes non-handi-

capped as far as his particular job is concerned. It is not a matter of coddling, but one of proper placement. The worker is fitted to the task and knows that a full day's work is expected of him.

Most individuals use less than 10 per cent of their potential efficiencies in normal pursuits. It is only in emergencies that we call upon our tremendous reserves of physical power and ability. In many cases a worker's physical defect acts as a tremendous stimulus to overcompensation, resulting in extraordinary physical ability. Adler developed a complete system of psychology on the basis of inferiority. He believed that the successful, the efficient and the aggressive individual was one who was compensating for some inferiority. The employer of handicapped workmen is putting that psychology into purposeful and gainful application.

Foremen report that handicapped workers are frequently a steadying influence in their departments. Their jobs mean more to them than to the normal workers. They have had more difficulty in getting employment and they value the right to work.

Office of Vocational Rehabilitation

The work of the Office of Vocational Rehabilitation and its participating State rehabilitation programs, has been growing steadily since it was established under the National Civilian Vocational Rehabilitation Act of 1920. Its services were greatly expanded by amendments to the original law by Congress in 1943. Today, under Public Law 113, the disabled civilian can obtain practically the same rehabilitation services as offered to the disabled veteran by the Veterans' Administration under Public Law 16, with the exception of pensions and subsidization of living expenses. The record of the federal-state rehabilitation programs is heartening but when the 43,000 persons who received such service in 1944 are compared to the one and one-half to two million whom the Office of Vocational Rehabilitation estimate are in urgent need of such service, it is woefully inadequate.

The Federal and State vocational rehabilitation programs alone, however, cannot meet our rehabilitation needs. Although they have both the funds and the authority, they are handicapped by the lack of training facilities to which they can refer their cases. These state vocational rehabilitation agencies do not do the actual rehabilitation themselves, but use existing public and private facilities such as schools, vocational

training courses, and on-the-job training on a fee basis.

Medical, surgical and diagnostic services are obtained by contract with groups, clinics and private physicians. Hospital care is purchased from existing hospitals. The same is true in physical restoration, which may include any type of medical or allied services that will aid in eliminating or substantially reducing an individual's disabilty as an employment handicap. These include medical, surgical or psychiatric service, physical and occupational therapy, hospitalization, dentistry, care in a convalescent or nursing home, drugs and supplies, and such prosthetic appliances as artificial limbs, braces, hearing aids, eyeglasses and dentures.

The funds and authority are available, but the facilities equipped for doing the actual job of rehabilitation are inadequate. Several national organizations are making efforts to stimulate public interest in rehabilitation by demonstrating to both the medical profession and the public what actually can be done by an integrated program of physical, mental, social and vocational adjustment.

One such group is the Baruch Committee on Physical Medicine, which is translating the experiences of the armed forces in rehabilitation into its civilian applications, and making this experience available to communities, medical schools, or organizations interested in establishing rehabilitation centers.

The Baruch Committee members have pointed out that rehabilitation cannot be done by segments. If a man has a hearing disability, has lost a leg, or has a cardiac condition, his disability affects all phases of his life. It has a bearing on his vocational opportunities, his family and social life, his recreation and his mental and emotional outlook. Individual disabilities cannot be treated in rehabilitation; the whole man must be considered.

Today there are a few specialized services to the handicapped which are doing excellent work in their limited fields. The number is so small that they can reach only a small fraction of those who need aid. Too many existing programs, however, can treat only one segment of a patient's problems. There is a great need for comprehensive, integrated community centers. Rather than a dozen small agencies each giving individual psychological assistance, occupational therapy, vocational training or social service, aid to the deaf, the blind, the orthopedically handicapped, the patient with a speech defect, or arrested tuberculosis,

or the cardiac, there needs to be one large community center where all the necessary services can be integrated to improve the quality and scope of service to the patient.

The Baruch Committee has outlined a plan for community rehabilitation centers that will furnish a complete service.[10] They have blueprinted a model rehabilitation center, outlining its mission, organization, components, physical set-up and its relationship to the medical and allied professions—industry, labor, social and governmental agencies—and to the community as a whole. The report provides communities with a pattern representing the ideas and experiences of both the armed services and leading civilian institutions and organizations.

Preventive medicine and curative medicine and surgery have made great advances. Their third phase of medical care—rehabilitation—has been neglected. Comprehensive rehabilitation programs have been established in the armed forces. The Veterans' Administration is organizing a similar service. The disabled civilian in a democracy deserves the same opportunity as the disabled Veteran.

It is not enough to get our patients out of bed. Our duty, as physicians, is terminated only when our patients are returned to productive living. The magnitude of the task is a staggering one, a challenge that must be accepted not only by the medical profession but by the democracy.

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CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

JUNE 5, 1946

BERNARD S. OPPENHEIMER, *Chairman*

* * *

*The Clinical Correlation of In-Vitro Penicillin Sensitivity Tests**

ERNA ALTURE-WERBER, PH.D., MARY KOZAK SHORE, *A.B.*,
EDITH C. MENKES, and LEO LOEWE

In-vitro penicillin sensitivity tests of organisms as a rule merely estimate the bacteriostatic activity of penicillin. The information gained from this type of test was not always helpful in establishing optimum dosage schedules for the treatment of diseases caused by penicillin inhibitable organisms. In actual practice, particularly in the treatment of subacute bacterial endocarditis, merely parallelling in the blood serum the in-vitro penicillin bacteriostatic activity did not consistently achieve effective therapeutic blood levels. As a result of clinical experience therefore the dictum was well founded that multiples of five to ten times the in-vitro sensitivity figure were essential for termination of the infection. It was subsequently suggested that "to be therapeutically effective, penicillin blood levels must be far in excess of the in-vitro bactericidal requirements" and that "inadequate dosage invites treatment failure and the organisms may acquire resistance that is so high as to render future therapeutic levels virtually unattainable."[1,2] It was early evident that there is both a bacteriostatic and a bactericidal zone of penicillin activity. While the arbitrary intensification of penicillin dosage in the treatment of subacute bacterial endocarditis was attended with greater clinical success, there were still sufficient treatment failures to justify intensive investigation for the causative factors. One result of this study was the discovery of a new type of non-hemolytic streptococcus, designated Streptococcus s.b.e.[3] The factors responsible for the refractory nature of this organism are under investigation and are not discernible in test tube studies per se. Laboratory techniques were devised to determine the bacteriostatic and minimal lethal dosage of penicillin for the infecting organisms. The routine use of these procedures has afforded an explanation for the failure of penicillin treatment with seemingly adequate dosage as judged by customary standards. Thus while the infecting non-hemolytic streptococcus of P.G., a patient with subacute bacterial endocarditis, had a bacteriostatic penicillin sensitivity of 0.008 Oxford units per cc. of test broth, a seven weeks span of therapy of 300,000 to 500,000 Oxford units of penicillin daily with average blood levels of 0.53 Oxford units per cc. failed to cure. A total of 22.4 million Oxford units was administered during this unsuccessful course of therapy. The answer was found in the determination of the minimum lethal dosage of penicillin for this causative organism, which proved to be 1 Oxford unit per cc. of test broth. When the daily penicillin dosage was lifted to 2 million Oxford units with resultant blood levels of 2 or more units per cc. of serum,

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the blood stream was sterilized and the infection was terminated. That subcurative doses of penicillin have a pronounced tendency to increase the resistance of infecting organisms was apparent in our series of 157 cases of subacute bacterial endocarditis treated with the combination of penicillin and heparin. This fundamental concept, the implications of which are now widely recognized, has been found to apply to infections in general.

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Repository Injection of Penicillin in Water-in-Oil Emulsion

Effect on Early Syphilis—A Preliminary Report

ALFRED COHN, THEODORE ROSENTHAL and ISAAK GRUNSTEIN

In previous investigations a method was developed to cure gonorrhea by a single intramuscular injection of penicillin in water-in-oil emulsion. The administration of penicillin in such a vehicle has been now applied for the treatment of early syphilis. It is hoped that this method which reduces the number of daily intramuscular injections to one or two, may open the way for the ambulatory treatment of syphilitic patients with penicillin.

A total of 35 male patients with early syphilitic infections received daily injections of penicillin in water-in-oil emulsion over a period of 5 days. The daily dose ranged from 400,000 to 1,000,000 Oxford units of penicillin, given intramuscularly either at 12 or 24 hour intervals.

After total dosages of 2,000,000 to 5,000,000 Oxford units respectively, definite clinical regression of the syphilitic lesions were observed among all patients at the end of active therapy.

Darkfield examinations initially positive for Treponema pallidum, were found negative 24 hours after the initiation of treatment in all of 11 cases examined.

Complete healing of the primary chancre at the fifth day of treatment was noticed in 19 patients and healing within a period of 13 to 90 days took place in 13 cases. Of the remaining 3 patients one showed a clinical relapse when reëxamined 65 days after treatment, and the other 2 patients were delinquent.

Complete involution of the secondary manifestations immediately following treatment was observed among a group of 12 patients and within a period of 11 days to 6 weeks in the remaining 3 patients. Similar involution of lymphadenitis occurred either shortly after treatment or 5 to 7 months later.

Titrated Wassermann reactions and flocculation tests (Kahn, Kline and Mazzini) were done on the serum of each patient before treatment and repeated each time the patient reported for reëxamination. Four initially negative Wassermann sera remained negative during a period of 1 to 12 months. The positive Wassermann tests of 16 patients reversed to negative within a period of 5 to 28 weeks. The sera of 2 other patients yielded persistently positive Wassermann and flocculation tests over a period of 8 to 10 months, while their corresponding spinal fluid tests done 6 months after treatment, were negative.

The initial spinal fluid examinations of all patients before treatment were negative. The spinal fluid of 14 patients reëxamined 6 months after treatment were also negative.

Ten cases were followed for a period up to 6 months. In this group there occurred the only clinical relapse observed thus far, 60 days after treatment. This patient suffered from sero-positive primary syphilis and was treated over a period of 5 days with single daily injections of penicillin in water-in-oil emulsion (900,000 Oxford units

the first day and 700,000 Oxford units daily for 4 days), simultaneously with a daily dose of 100,000 Oxford units in saline.

Fourteen patients remain under observation for period of 6 to 10 months; none show any signs of clinical relapse; there are, however, 2 patients with persistent positive serologic reaction requiring further observation, and a third patient with secondary syphilis whose serologic test reversed from negative to positive 8 months after treatment.

Injections of penicillin in the oily vehicle did not produce any serious side effects except transitory pains of varying intensity at the site of injection. Herxheimer reactions of a mild degree occurred in most cases.

For purposes of comparison two patients were treated with corresponding single daily injections of penicillin (total dosages of 2,000,000 and 4,200,000 Oxford units) in saline alone; both patients suffered clinical relapses within 2 and 3 months respectively.

Comparison of penicillin serum and urine levels in patients receiving first a single injection of penicillin in saline and 5 days later a single injection of identical amounts of penicillin in water-in-oil emulsions shows the following findings:

1. No essential difference in the duration and height of penicillin serum levels was noticeable among the 2 groups.

2. The 24-hour urine levels of patients who received single injections of penicillin in water-in-oil emulsion were twenty to one thousand fold higher than the urine levels of the patients after single injections of identical amounts of penicillin in water.

3. These findings correlated with clinical results may indicate that the administration of penicillin in water-in-oil emulsion prolongs the therapeutic effect of the antibiotic agent within the body, even though assayable penicillin serum levels could not be detected consistently.

Four patients received oral penicillin treatment. Of three receiving 6,000,000 Oxford units over a period of 6 to 10 days, 2 remain under observation. They are completely negative both clinically and serologically for a period up to 10 months. The fourth patient received a total dosage of 12,000,000 Oxford units over a period of 10 days, and displayed a clinical relapse after 68 days.

* * *

Galactose Removal Constant

An Expression of Galactose Disappearance From the Blood Stream: Its Application As A Test For Liver Function[*]

HENRY COLCHER, ARTHUR J. PATEK, JR., AND FORREST E. KENDALL

The rate of disappearance of galactose from the blood stream after a rapid intravenous injection was studied in 64 patients with and without liver diseases. A 50 per cent galactose solution was injected intravenously in amounts corresponding to 0.5 gm. per kilo body weight. Blood specimens were obtained before and at 15 minute intervals after the injection for a period of 90 minutes. Urine was collected as voided over a 4-hour period. The determination of blood galactose was based upon Benedict's method for blood sugar after removal of glucose by fermentation according to the method of Raymond and Bianco.

When the logarithm of blood galactose concentration is plotted against time a straight line is obtained. This straight line may be interpreted to indicate that the rate of removal of galactose from the blood is directly proportional to the concentration in the blood. By use of the following equation a constant, K, was calculated.

$$K = \frac{2.3\ (\log C_1 - \log C_2)}{t_2 - t_1}$$

[*] From the Research Service, First (Columbia) Division, Goldwater Memorial Hospital, Department of Hospitals, and the Department of Medicine, College of Physicians and Surgeons, Columbia University.

C_1 and C_2 are the concentrations of blood galactose (in mg./100 cc.) at times, t_1 and t_2 expressed in minutes. K represents the fraction of the total amount of galactose present at any given time that is removed from the blood each minute. If K is multiplied by 100 the numerical value obtained expresses the percentage of the amount present that is removed each minute. This might be called the Galactose Removal Constant or G.R.C.

The Galactose Removal Constant can be calculated with sufficient accuracy from two blood specimens obtained at 15 and 45 minutes after intravenous injection. Under these conditions the constant may be calculated by the following equation:

$$\text{G.R.C.} = 7.6\ (\log \text{conc. at 15 min.} - \log \text{conc. at 45 min.})$$

The value of G.R.C. varied between 4.2 and 9.5 in 10 controls and was below 4 in 43 patients with parenchymal liver damage (26 patients with cirrhosis of the liver, 7 cases of hepatitis, and 10 patients with chronic passive congestion of the liver). In one patient with acute hepatitis, the value of G.R.C. was 1.9 and 1.94 on the 4th and 14th day of illness and returned to normal value of 6.2 three months after clinical recovery.

A series of determinations pertaining to liver functions were performed simultaneously with the galactose test on all patients. These included serum protein partitions, serum bilirubin, plasma prothrombin, cephalin cholesterol flocculation, bromsulphalein dye retention and urinary urobilinogen excretion. There was a good correlation between the values of galactose removal constant and other liver function tests.

* * *

*The Etiologic Agent of Pemphigus Vulgaris**

ARTHUR W. GRACE

INTRODUCTION

In a search for additional data upon the etiologic agent of pemphigus vulgaris,[1,2] pathologic and control materials were inoculated into the brains of x-irradiated and normal mice.

MATERIALS

The inocula consisted of:

A. *Materials obtained from persons suffering from pemphigus vulgaris:*

Twelve blisters arising spontaneously; 3 cantharides-induced blisters; 8 cerebrospinal fluids; 6 whole bloods; 1 blood plasma; 5 blood sera; 2 washed blood cells; 3 tissues obtained at autopsy.

B. *Materials obtained from persons suffering from diseases other than pemphigus vulgaris:*

Three blisters arising spontaneously; 1 cantharides-induced blister.

C. *Materials obtained from normal persons:*

Three cantharides-induced blisters; 2 blood sera.

D. *Materials obtained from mice:*

Seventy-eight irradiated mouse brains containing heat-inactivated RP strain of virus; 15 irradiated normal mouse brains.

RESULTS

Nine strains of non-bacterial agents, transmissible to mice, were obtained from 7 persons suffering from pemphigus vulgaris. Four of the strains were derived from spontaneous blisters, 3 from cerebrospinal fluids and 2 from blood sera. No transmissible agents were obtained from any of the other materials. The strains were transmitted for the following number of passages respectively: 242, 11, 5, 4, 1, 1, 1, 1, 1. No attempt was made to transmit 3 of the ma-

* From the New York Hospital and the Department of Medicine, Cornell University Medical College and the Long Island College Hospital and the Department of Dermatology and Syphilology, Long Island College of Medicine. Aided by grants from the John and Mary R. Markle Foundation and from the Dazian Foundation for Medical Research.

terials for more than 1 passage.

The criterion of the presence of the agent was the appearance in the brains of infected mice of discrete and diffuse, macroscopic and microscopic, collections of polymorphonuclear leukocytes. In some instances, the spinal cord and meninges were also involved in the same histologic change. Sick animals whose brains did not show this change were not regarded as having been infected.

Close study was made of the RP strain of virus, which was transmitted for 242 passages, with the following results:

a. The virus is unlike any spontaneous mouse virus hitherto described.

b. Neutralization experiments were performed with sera obtained from 10 normal persons and from 13 persons suffering from pemphigus vulgaris. Some degree of neutralization was obtained with some normal sera but definitely higher degrees of (and in one case, complete) neutralization were obtained with pemphigus sera. The serum from another case of pemphigus showed the development of a high degree of neutralization coincident with clinical remission and its disappearance in a relapse which terminated in the death of the patient.

c. Rabbits received virus by corneal scarification and by intradermal, intracerebral, intratesticular and intraperitoneal routes. Guinea pigs were inoculated subcutaneously, intracerebrally and intraperitoneally. No pathologic changes were produced in the animals. The virus, therefore, was not that of herpes, vaccinia, rabies, choriomeningitis or lymphogranuloma venereum.

d. No growth occurred in medium used for the growth of pleuropneumonia-like organisms.

e. Experiments in which an inoculum was employed whose concentration was 20 times that used for infection of irradiated mice showed that, while infection of non-irradiated mice occurred readily, it was impossible to maintain the virus for more than 3 or 4 passages in non-irradiated mice.

f. Vesicles accompanied with intense ectodermal, mesodermal and entodermal cellular reaction were produced by depositing the virus on the chorioallantoic membrane of the developing chick.

CONCLUSION

The data gathered in this study warrant the conclusion that the virus whose characteristics are outlined in this paper is the etiologic agent of pemphigus vulgaris.

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* * *

Some Pharmacological and Clinical Experiences with Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl)

THOMAS H. MCGAVACK, HERBERT ELIAS AND LINN J. BOYD

The action of dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) was studied in 60 normal subjects and in more than 200 patients with various forms of allergic and other diseases in which sudden releases of histamine may play a pathogenetic role.

The various systems of the body were systematically checked in the 'normal' subjects and in some of the patients for both physiological and toxic actions of the drug.

The data obtained has been correlated under three main headings: (1) physiological and pharmacological effects of the drug as observed in "screening" tests for the functions of the various systems of the body in all of the 'normal' subjects and in some of the patients; (2) the therapeutic range of activity of benadryl; (3) the nature and frequency of toxic reactions.

1. ***Effects of benadryl upon various bodily systems and functions.*** The positive

data which were obtained in the study of 'normal' subjects and some of the patients indicated:

a. A depression of the secretion of gastric acid in 19 of 21 subjects studied, noticeable witn doses of 150 mg. daily, and occasionally reaching a state of complete suppression when 400 mg. were administered daily.

b. A depression of the dermal response to histamine in all of 20 normal subjects and in 7 patients studied. There was complete suppression of the response when patients were kept on from 300 to 400 mg. of drug daily for several weeks. Reactions to the injection of histamine were continuously abolished promptly by the intravenous administration of 20 mg. of benadryl.

c. An atropine-like action of topically applied benadryl upon the pupil of the eye, maximal in degree by the end of 1 hour. This was hastened not increased by epinephrine. Benadryl increased the action of atropine and decreased that of eserine.

d. The development of orthostatic hypotension in approximately 8 per cent of all subjects studied.

e. A moderate decrease in the capillary permeability of subjects receiving doses of 300 to 400 mg. of benadryl daily.

2. *The therapeutic range of activity of benadryl.* Benadryl proved to be most highly effective for the control of acute and chronic urticaria, angio-neurotic edema, allergic eczema, hay fever and vasomotor rhinitis. Good but less reliable effects were observed in patients with bronchial asthma, neurodermatitis, dysmenorrhea and spastic colon. In many instances relief was afforded patients who suffered from Ménière's syndrome, migraine, 'intractable' insomnia, a variety of gastrointestinal neuroses (other than spastic colon), and cardiac asthma. However, the results do not warrant conclusive statements regarding the routine usefulness of the drug in these conditions. A questionable influence upon essential hypertension and the tremor of paralysis agitans has been noted. In several other conditions of widely diverse nature, no beneficial action could be demonstrated.

3. *The nature and frequency of toxic reactions.* Drowsiness was the most frequent and most distressing untoward manifestation of the action of benadryl. It was usually most marked after the first dose or doses of the drug; later a "tolerance" was commonly established. A single dose of 50 mg. has evoked a severe response, necessitating the use of coffee or benzedrine sulfate to keep the subject awake. Other unpleasant symptoms in the order of their frequency included dizziness, blurring of vision, dryness of the mouth, and an "all gone feeling" at the pit of the stomach. None of the reactions observed in any way endangered the subject's life or health, and all disappeared in from one-half to several hours after discontinuing the drug. Moreover, as a rule the drug could be resumed without untoward effect by stepping up the dose gradually.

It was concluded that benadryl is a powerful antihistamine agent which has in addition weaker but definite antispasmodic activity of an atropine-like type.

* * *

The Clinical Evolution of Vascular Damage in Diabetes Mellitus

HENRY DOLGER

The long recognized association of vascular damage with diabetes mellitus was emphasized in 1936 by Kimmelstiel and Wilson in a report on intercapillary glomerulosclerosis. Our observations indicate that this triad of retinopathy, hypertension, and albuminuria is more than a terminal "pathological" syndrome.

When diabetic patients, young and old, mild and severe, were scrutinized carefully over a period of years, such vascular damage was found in every instance. When 200 patients below fifty years of age were followed dilıgently for 25 years, not one escaped retinal hemorrhages, albuminuria and/or hypertension in varying degree. The

group investigated consisted of 16 whose age of onset of diabetes was below 10 years; 39 whose age of onset was between 10 and 20 years; 22 between 20 and 30 years; 43 between 30 and 40 years; and 80 between 40 and 50 years. There was no preëxisting hypertension in any of these persons.

Retinal hemorrhage was the predominant lesion when diligent search was made routinely, and it often preceded the appearance of albuminuria and/or hypertension. When this sequence was not observed it could probably be attributed to failure to notice transient hemorrhages which had resolved in the interval between examinations. All three lesions appeared in the patients regardless of the age of onset or degree of severity of the diabetes, the need for insulin, the type of diabetic "control" or diet employed, the blood cholesterol levels, or the absence of x-ray evidence of arterial calcification.

Careful repeated examinations of the eye grounds, blood pressure, and urine for albumin revealed *no* single instance where the diabetes had lasted 25 years in which the patient escaped the development of vascular damage. Some presented rapid progression into the full blown clinical syndrome of intercapillary glomerulosclerosis frequently with blindness. In the majority, however, the lesions progressed slowly with accelerated damage occasionally in isolated viscera and tissues such as renal, coronary and cerebral vessels, etc. The finding of specific renal vascular lesions on postmortem examination in 68 per cent of all diabetic patients was reported in 1944 by Laipply, Eitzes, and Dutra. This may now be considered a low estimate in view of our finding of vascular lesions in 100 per cent of all diabetics followed 25 years. In the middle age groups, the damage often appeared within 5 years of the onset of diabetes and not infrequently was noted coincidental with the onset. In a few instances, the lesion seemed to antedate the onset of clinically detectable diabetes.

Every diabetic would seem at present to be doomed to the inexorable development of vascular damage despite the benefit of insulin in prolonging life. At most, 25 years of freedom from arteriosclerosis can be offered even to the juvenile diabetic. The prevention of these inevitable sequelae are a challenge to the future.

* * *

Insulin Resistance: A Case Study

THOMAS H. MCGAVACK, SOLOMON D. KLOTZ, MILDRED VOGEL *and* JAMES F. HART

A 64-year old man with diabetes of 7 years duration has been observed in 3 periods of "insulin resistance" with severe ketonuria and glycosuria, during which a "peak" daily dose of insulin has been 3250, 1320 (400 intravenously), and 500 units respectively. Between these periods the patient's urine has been free of sugar and acetone without exogenous insulin. During the third period of resistance, the presence of allergic antibodies has been demonstrated repeatedly by the use of the Kustner-Praus-nitz method for the passive transfer of sensitivity. Such reactions disappeared within 10 weeks after insulin was discontinued and reappeared within 10 days after its resumption.

Other protective substances of a directly anti-insulin or anti-hypoglycemic nature were sought for in the blood of the patient. However, repeated tests failed to show that his blood was capable of protecting mice from otherwise fatal doses of insulin.

Following an acute pancreatitis associated with the formation of a pseudo-cyst, the patient's sensitivity to insulin has become normal, and the allergic reactions previously noted can no longer be demonstrated.

It is concluded that under certain circumstances insulin may act as an allergen; the development of antibodies may be so great that severe resistance to the action of insulin results. The data are discussed in relation to previous concepts of insulin resistance as revealed in the literature.

Experiences with Folic Acid in Macrocytic Anemia

LEO M. MEYER

Data are presented concerning the use of folic acid in the treatment of 7 cases of pernicious anemia. Three of the patients received folic acid in doses of 50 mg. orally or 20 mg. intramuscularly daily. Clinical improvement with relief of symptoms and increases in hemoglobin, red cells and reticulocytes followed. However, complete hematological remissions could not be obtained, and 2 of the patients showed progression of their neurological signs and symptoms. The third died on the 37th day of bronchopneumonia. Four other patients were treated with combinations of 5 or 10 mg. of folic acid plus ½ unit of liver extract intramuscularly, daily. On this regime symptoms were relieved and blood pictures became normal. Reticulocytes rose to levels greater than those anticipated with liver alone and 2 of the patients with neurological signs were distinctly improved.

The author concludes that folic acid, by itself, fails to raise the Hb and red cells to normal levels and is unable to prevent the development or progression of signs of subacute combined sclerosis. However, the combination folic acid and small doses of liver produces a more rapid rise in the Hb and RBC with higher reticulocytosis and is effective in preventing and curing involvement of the central nervous system.

* * *

*A Study of Histochemically Demonstrable Liver Phosphatase in Experimental Obstructive Jaundice and in Human Postmortem Material**

M. WACHSTEIN and F. G. ZAK

Methods capable of demonstrating enzymatic reactions in tissue sections have opened a new approach to the study of various biological problems. In view of the marked changes in serum alkaline phosphatase activity occurring in liver disease, a study of this enzyme in liver sections under experimental conditions, as well as in postmortem material, was undertaken. Gomori's method, as modified by Kabat and Furth with some minor alterations was used.

Little stainable phosphatase was present in the livers of normal rats and mice. Increase in cytoplasmic alkaline phosphatase activity in the atrophic liver cells of starved, in the hydrophic liver cells of protein depleted mice, and to a lesser degree of rats, has been described in a previous paper (*Arch. Path.* 1945, *40*,57). In the livers of animals poisoned by phosphorus, chloroform and carbon-tetrachloride there was no significant increase of phosphatase in necrotic cells.

In continuation of these experiments the common bile duct was ligated in 9 dogs after an initial biopsy had been taken. In the dog liver the bile capillaries showed conspicuous phosphatase activity. After the ligation there occurred a marked rise in serum alkaline phosphatase as described by various investigators. There was marked dilatation of the bile capillaries, increasing with the duration of the experiment. This widening apparently was caused by the accumulation of phosphatase in the liver cells around these structures. Considerable dilatation of bile capillaries was also seen in the livers of several rabbits 4 to 5 days after the ligation of the common bile duct.

The postmortem material included both

* From the Laboratories of the E. A. Horton Memorial Hospital, Middletown, New York and Mt. Sinai Hospital, New York.

sections from livers not involved by disease, and sections from livers which had been the seat of various pathological processes. In liver sections from patients whose death was due to various causes and in which no significant gross or microscopic changes were found, only little alkaline phosphatase activity was demonstrable in the liver cells, while the sinusoids, as well as the bile capillaries, showed a varying degree of activity. In 8 cases of obstructive jaundice there was dilatation of bile capillaries which, however, was absent in the 2 remaining instances. The degree and extent of the widening of the bile capillaries as seen in these preparations stained for alkaline phosphatase activity varied considerably. It was only focal in some and fairly uniform in others. Necrotic liver cells in these livers as well as in a number of other livers in which extensive necrosis had occurred, did not show increase in enzymatic activity. In a case of subacute yellow atrophy and in a case of toxic (post-necrotic) cirrhosis, there was conspicuous activity in the proliferating connective tissue and the infiltrating round cells. Marked staining of the connective tissue occurred also in some cases of Laennec cirrhosis while in other cases, obviously in a more quiescent stage, the connective tissue showed only little activity. In several cases in which hepato-cellular changes were superimposed and in which jaundice as well as increase in serum alkaline phosphatase had been present, focal dilatation of bile capillaries was seen while otherwise the liver cells did not show any alteration in their enzymatic activity. In several livers of patients who died from various causes (cardiac failure, glomerulo-nephritis, etc.) but without clinical and anatomical evidence of significant liver disease, considerable increase in cytoplasmic alkaline phosphatase activity was found.

The origin of the increased serum alkaline phosphatase in liver damage is still controversial. The behavior of histochemically demonstrable phosphatase activity in the liver under experimental conditions and in human postmortem material favors the assumption that this rise is due not to increased production in the diseased liver, but rather to the inability of the liver cells to excrete the enzyme. This may be caused either by external obstruction, or by cellular dysfunction. The blood level of alkaline phosphatase probably is in addition influenced by extra-hepatic factors, since phosphatase can be excreted in the pancreatic juice and through the intestinal tract and in addition through the kidneys in some species. Disturbances in calcium and phosphor metabolism in hepatic disease may influence the production of this enzyme in the osseous system.

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LIBRARY NOTES

*THE "HERNIA CONGENITA" AND AN ACCOUNT OF THE CONTROVERSY IT PROVOKED BETWEEN WILLIAM HUNTER AND PERCIVALL POTT**

FENWICK BEEKMAN

"PERHAPS it may be as sound philosophy to say, that all the actions of men are directed to some good end, as it is to subscribe to an opinion which has prevailed among naturalists, that, in the works of nature, nothing is absolutely without its use. Literary disputes are disagreeable to the greatest part of mankind; and the disputants are, for the most part, condemned by the world. Yet it is reasonable to think, that even these disputes answer some good purpose. By engaging the passions of men more warmly, they rouze a spirit of emulation, and give a spur to enquiry.

"It is remarkable, that there is scarce a considerable character in anatomy, that is not connected with some warm controversy. Anatomists have ever been engaged in contention. And indeed, if a man has not such a degree of enthusiasm, and love of the art, as will make him impatient of unreasonable opposition, and of encroachments upon his discoveries and his reputation, he will hardly become considerable in anatomy, or in any other branch of natural Knowledge.

"These reflections afford some comfort to me, who unfortunately have been already engaged in two public disputes." (Hunter, Wm.—*A Supplement to the First Part of Medical Commentaries*, p. iii.) So writes William Hunter in *The Introduction* to his accusation of plagiarism against Percivall Pott. At the time he brought this charge against his friend and fellow practitioner he was but concluding long and heated controversies over priorities in anatomical discoveries with his former teacher and friend, the venerable Alexander Monro of Edinburgh, for whose learning he held great respect. But in William Hunt-

* The biographers of both William Hunter and Percivall Pott have written little of this dispute, merely mentioning its occurrence.

er's opinion, the establishment of justice in anatomical discoveries, by placing credit where he thought it belonged, surmounted all other considerations, whether they were ties of friendship, blood relationship, or the veneration for an old master. He writes: "A Controversy relating to any improvement or discovery in the arts, when there are complaints of unfair dealing, is an aukward [sic.] subject for a party principally concerned. The writer must plead his own cause; and where he thinks himself in the right, and ill-treated, he will be led to speak in his own favour, and to the prejudice of another person; both which a man of an ingenuous turn of mind would willingly avoid." (Hunter, Wm.—*Medical Commentaries,* p. v.) Continuing, he informs us that a writer in such a dispute may appear to magnify trifles and be looked down upon as a petty person. And finally he writes:

> "Another circumstance, as unpleasant as either of those already mentioned, is, that in order to do justice to the cause, it may be necessary to say many things, which an author would wish to avoid; he may be obliged either to suppress his evidence, or to call upon his friends, and publish matter of private conversation; in short, to mention many things, which though, for some reason or other, it may be disagreeable to relate them, are yet necessary in the defence of truth." *(ibid.)*

With these opinions of William Hunter before us, we may now take up the story of a particular controversy, between him and Percivall Pott.

During the winter of 1755-56, John Hunter is found busily investigating the descent of the testis in the foetus during the late months of intra-uterine gestation. This subject had been first brought to the attention of his brother, during the year 1748, by Samuel Sharp, who enquired of William Hunter whether when "dissecting ruptures' he "had ever found the intestine in the same bag, and in contact with the *testis.*" (Hunter, Wm.—*Medical Commentaries,* p.70.) A few weeks later a body of a man with bilateral hernia having come under William Hunter's observation, he called Mr. Sharp and together they dissected out these ruptures; "as soon as the hernial sac of the right side was laid open," writes William Hunter, "we saw the *testis* lying bare, in the bottom of its cavity.—Then we dissected the rupture of the left side; and there it was as indisputable that the bottom of the hernial sac was situated upon the outside of the *tunica vaginalis propria,* or, in

other words, that these two bags were distinct, and without any communication; and that the intestine in such a rupture could not have come in contact with the *testis*, unless a laceration had been produced both in the hernial sac, and in the *tunica vaginalis propria*. We therefore concluded that such a laceration of those bags had actually happened to the rupture on the right side, and that it must happen in all ruptures where the *testis* is found in contact with the intestine." (*ibid.* p.71.) So sure was Sharp that a congenital hernia (the name by which it is known today) was actually due to a rupture or laceration of a simple hernia sac into that of the tunica vaginalis, that he wrote, two years later, "it is evident to me that notwithstanding the *Peritoneum* may at first fall down with the *Viscera*, yet in length of time it may also be ruptur'd, because I have found the *Intestine* and *Omentum* within the *Tunica Vaginalis* of the Testicle, and in contact with the Testicle itself, which they could not possibly have been, if they were invelop'd in a portion of the *Peritoneum:* However this Circumstance occurs but rarely, for we usually find the *Viscera* within a *Prolapsus* of the *Peritoneum*, which Prolapsus is now known by the Name of the *Herniary Sack*." (Sharp, Samuel–*A Critical Enquiry*, etc., p.3.)

The Hunters did nothing further to unravel the mystery surrounding the cause of oblique inguinal hernia until late in the year 1755, soon after William had read Albrecht von Haller's observations on the *hernia congenita*, which appeared in the newly published *Opuscula Pathologica*. From this communication he learned much that was new to him concerning the subject. Some of Haller's opinions were, that in the foetus the testicles are "lodged in the cellular membrane of the loins, contiguous to the kidnies." "The descent of the testicles is gradual, and after some time, which has not hitherto been determined, they fall down into the Scrotum, always behind the Peritoneum, as now they are situated under it. The cause of this progression seems to be owing to the force of respiration, and the action of the abdominal muscles." (From this it appears that Haller believed the descent of the testicles occurred after birth.) And finally William Hunter learned of Haller's opinion concerning the development of a hernia following the descent of the testicle, as given below:

> "Hence, if I am not mistaken, the manner how congenial Hernias are formed, very plain appears. The process of the Peritoneum under the kidnies is open, in order to receive the testicle,

> and that being pressed downwards, as usual, the testicle at the same time is carried along with it, and both together fall down into the Scrotum. But as in these bodies the testicles are contained in one and the same bag with the intestines, it is not at all singular or surprizing that a slight impulse should force down the latter into this open space."* (Haller, Albert–*Pathological Observations*, p. 59.)

Speaking of this newly acquired knowledge in later years, William Hunter said: "it struck my imagination that the state of the *testis* in the *foetus* and its descent from the *abdomen* into the *scrotum* would explain several things concerning ruptures and the *hydrocele*, and particularly that observation which Mr. Sharp had communicated to me, viz., that in ruptures the intestine is sometimes in contact with the *testis*." (Hunter, Wm.–*Medical Commentaries*, p.72.) Having communicated his thoughts to his brother, John had then begun an investigation to ascertain "the state of the *testis* before and after birth, and the state of ruptures in children." *(ibid.)* John Hunter was not, however, entirely ignorant of this subject, as his brother informs us that: "Several years before Haller's Opuscula Pathologica were published, my brother informed me, that in examining the contents of the abdomen of a child, still born, about the seventh or eighth month, he found both the testicles lying in that cavity, and mentioned the circumstances with some degree of surprise." (Hunter, John–*Observations on Certain Parts of the Animal Oeconomy*, p.1.) During this winter (1755-1756), John Hunter prepared a number of specimens to demonstrate the stages in the descent of the testis, from dissections made upon foetuses of different ages.** From these specimens, the artist, I. V. Riemsdyk, made numerous drawings, from which three plates were finally prepared that later were used as illustrations for John Hunter's paper, that first appeared in William Hunter's *Medical Commentaries* during the year 1762, with the title of "Observations on the State of the Testis in the

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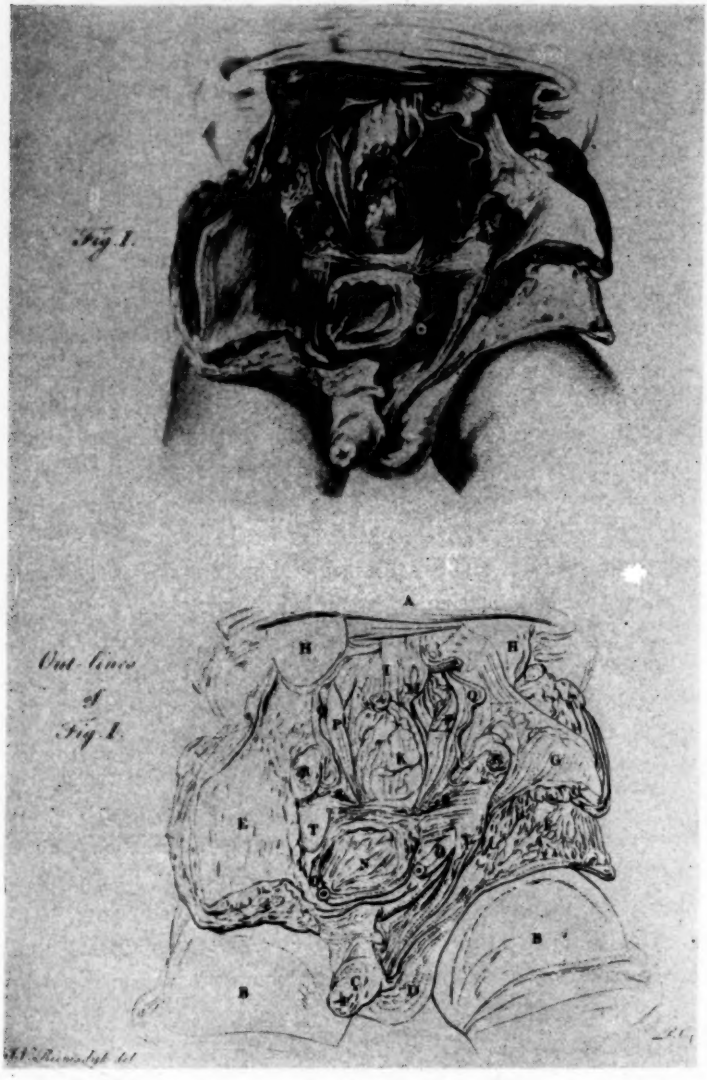
* Sir Richard Owen writes that: "Although Haller was in doubt as to the exact period of the descent of the testis, and in error as to the cause of that phenomenon, yet he accurately describes, in the original paper here alluded to, the original relations of the gland to the peritoneum and abdominal viscera, and the formation of the tunica vaginalis, and thus applies the facts which he had discovered to the explanation of the disease he was considering." (*The Works of John Hunter.* Edited by Jas. F. Palmer, Vol. IV: p.2, f.n.).

**There are eight specimens illustrating the descent of the testis in the Hunterian anatomical museum of the University of Glasgow. John H. Teacher, in the *Catalogue of the Anatomical and Pathological Preparations of Dr. William Hunter in the Hunterian Museum, University of Glasgow,* Vol. II. p.558, writes: "The specimens [42-60] from which Plate I. was taken were readily identified; but as to that (or those) from which Plates II. and III. were drawn there is some doubt, there being none which correspond exactly." The visitor to Glasgow is well repaid if he seeks out these specimens (see illustration), which are not only of historical interest, but may still be studied with value from an anatomical standpoint.



"Fig. I." from John Hunter's *Observations on the State of the Testis in the Foetus, and on the Hernia Congenita.* Representing "the testes within the abdomen, in an abortive foetus of about six months."

Foetus and in the Hernia Congenita", and later was republished, with only minor additions, in the year 1786, in John Hunter's *Observations on Certain Parts of the Animal Oeconomy,* under the heading of "A Description of the Situation of the Testis in the Foetus, with its Descent into the Scrotum".

This description of the descent of the testis, together with explanations for the cause of abnormalities that occasionally occur, as portrayed by John Hunter in this article, his first written presentation, is given most accurately in anatomical detail, in which particular stress is paid to the blood supply. With the exception of a few additional facts that have been only recently discovered, this work still stands as authority. Besides the anatomical facts, he describes, most minutely, each step occurring during the progress of descent, showing the manner in which the testicle carries a pouch of peritoneum before it and how the distal portion of this pouch normally isolates itself from the peritoneal cavity, in order to form the tunica vaginalis. The descent, he informs us, occurs before the time of birth (a statement in which he differs from Haller) and he writes:

> "From this original situation within the *abdomen* the *testis* is afterwards moved to its destined station in the *scrotum.* It is the more difficult to ascertain the exact time of this motion, as we hardly ever know the exact age of our subject. According to the observations which I have made it seems to happen sooner in some instances than in others, but generally about the eighth month. In the seventh month I have commonly found the *testis* in the *abdomen,* and in the ninth I have as commonly found it in the upper part of the *scrotum.*" (Hunter, William—*Medical Commentaries,* p.80.)

He also shows that if the distal portion of this peritoneal pouch is not isolated, a congenital hernia sac or an infantile hydrocele persists. He mentions further that a fixed portion of the intestine might occasionally be drawn down into the scrotum as a part of the wall of the pouch of peritoneum (a condition which today we know as a sliding hernia). Finally, he differentiates between the non-descent of the testis and a displaced testis. In this part of his paper he lays down several important suppositions concerning non-descent of the testicle, which have as yet not been disproved. "It is not easy to ascertain the cause of this failure in the descent of the testicle"; he writes, "but I am inclined to suspect

that the fault originates in the testicles themselves." (Hunter, J.—*Animal Oeconomy*, p.15.) "When both testicles remain through life in the belly, I believe that they are exceedingly imperfect, and incapable of performing the natural functions of those organs; and this imperfection prevents the disposition for their descent taking place." (*ibid*—p.18.)

William Hunter informs us that six years before the publication of *Medical Commentaries*, in April 1756 when he was concluding his lectures for the season with a course on "the chirurgical operations, I gave a very general account of my brother's observations, and shewed both the drawings of Fig. II. which was then finished, and the subject from which it was made." (*Medical Commentaries*, p.72.) Because of this demonstration before his class, William Hunter assumed, it seems, that he had established his right to priority for describing the *hernia congenita*. No wonder he was both surprised and irritated, during the following June or July, to receive from his friend, Percivall Pott, a copy of the latter's book, *A Treatise on Ruptures*, in which he found a discussion of the *hernia congenita*, without credit being given to either himself or his brother for their investigations upon this subject.

> "In the preface I found that he had done me the honour of adding my name to a very respectable list [William Hunter indignantly writes]; and I imagined that this compliment was meant as a very kind return for the respect which I had wished to shew him upon every occasion, and particularly for what had passed between us some time before, at a meeting for examining the nature of ruptures, and the state of the parts concerned: for when he began to compose his treatise (as I presume, because, though he said nothing to me of such an intention, I soon after heard of it among his friends) he desired that we might examine those things in the first proper subject which I could apply to that purpose." (*ibid*.—p.73.)

At this meeting, William Hunter tells us, he demonstrated his ideas to Pott upon a body on which his brother, John, was at that time dissecting. The date of this meeting I think must have been immediately preceding the middle of January 1756, for about that time Percivall Pott was thrown from his horse, sustaining a compound fracture of the leg. "During the leisure of his necessary confinement," from this injury, Pott's son-in-law tells us, "he planned, and partly executed his

treatise upon ruptures, which was completed by the latter end of the year." (Earle, Sir James—*A Short Account of the Life of Mr. Pott*, p.xv.)

The appearance of a new publication by Pott in March 1757, entitled *An Account of a Particular Kind of Rupture Frequently attendant upon New-Born Children*, did much to make matters worse, and precipitated a disgraceful altercation between the two men. In this treatise of forty-one pages, Pott presents his views upon the *hernia congenita* without even mentioning the Hunters.

A review of this book, appearing in the *Critical Review* of March 1757, in all probability written by William Hunter's friend Tobias Smollet, insinuates that Pott had borrowed the material for his work from Haller and the Hunters. Referring to these accusations, the reviewer writes:

> "He [Mr. Pott] quotes Mr. *Cheselden* and Mr. Sharp, and himself in his last years production upon ruptures, to shew that though the facts had been known, yet the theory, or true cause of the contiguity of the gut and testicle had not been understood; but he does not tell us that Dr. *Haller*, in his Opuscula Pathologica (which we gave an account of last year) has anticipated this discovery, in the account he gives of the congenital rupture. He has likewise the misfortune to be under suspicion of having learned all that he has published upon this subject at second hand, and imperfectly from Dr. *Hunter's* lectures. We are informed, by a letter from one that calls himself a pupil of Dr. Hunter, that this celebrated anatomist has, in his three last courses, explained fully everything in Mr. Pott's book; that he shewed, at his lectures, not only preparations of the parts, but drawings of them which his brother had provided, in order, with proper opportunity, to publish the observations which he had made upon this subject. This pupil further adds, that Dr. *Hunter* complained of Mr. *Pott's* publication, and appealed to many gentlemen, as well as to Mr. *Pott* himself, that he had above a twelve month ago made no secret of the discovery."

In appealing to Percivall Pott "to clear up these disagreeable appearances", Hunter presents his view on this accusation of plagiarism, as follows:

> "In my autumn course of lectures, 1756, (and indeed in every

course, which I have read since that time) I demonstrated the principal things contained in my brother's account of the *testes* in the *foetus;* and I particularly explained that species of rupture in which the intestine is found in contact with the *testis.* This circumstance of the disease, which had puzzled Mr. Sharp and Mr. Cheselden as well as myself, and which even Mr. Pott regarded as a *lusus naturae* [an accident], was now rendered perfectly intelligible. The discovery was become the novelty of the time among students in London, and other inquirers after anatomical improvements; and many gentlemen of my acquaintance desired to see the preparations which my brother had made; and among the rest my friend Mr. Pott did us that honour, one day during that course of lectures. I was not present. My brother shewed him the preparations with great readiness, and explained to him my hypothesis of the contiguity of the intestine and *testis* in some ruptures. Mr. Pott said nothing at that time of an intention to write upon the subject; but, some weeks afterwards, it appeared, by a public advertisement, that he was soon to publish a treatise on that species of rupture. I was much surprized; however, I thought it proper to say but little, till I should see how he treated the subject. The treatise came out in the month of March, 1757.—It hardly contained one new idea. It was what any of my pupils might have written; (for the cases given in the end supported only an uncontested fact) and yet neither my brother's name, nor mine was mentioned. It bore strong marks of *secondhand* observation, and of a *time*-serving hurry in the composition." (Hunter, Wm.—*Medical Commentaries,* p.89.)

Percivall Pott's defense to these charges, made against him in the article appearing in the *Critical Review* for March 1757 and by William Hunter in *Medical Commentaries* published in 1762, was not long forthcoming; for in October, 1763, a second edition of *A Treatise on Ruptures* came off the press. This contained a chapter giving an account of his side of the dispute. It is creditable to Pott that he shows so little rancor against his vilifiers, for he merely makes simple denial of all the charges. His language, in fact, is so restrained that it aroused a spirit of justice within William Hunter; so much so that he wrote: "He has treated me, for the most part, with the language of a gentleman, for which I thank him. I have indeed, received some *incision* at his hand,

but little *butchery;* and I have been so much used to meet with the latter, that I am the more sensible of his lenity." (Hunter, Wm.–*A Supplement to the First Part of Medical Commentaries,* p.v.)

Before starting upon the arguments for his defense, Pott apologizes to his readers for entering the dispute, which was, it seems, most distasteful to him, by writing as follows:

> "I am perfectly sensible of how very little importance all these disputes are to all other people except the disputents themselves; and how very difficult it is for any man to tell what relates merely to himself, in such manner as not to tire and disgust those who have no interest in it; but as I have been (to use Dr. Hunter's own words) *wantonly*, and I cannot help thinking malevolently attacked, and treated in a manner which appears to me highly ungenerous, not to say illiberal, I hope the reader will indulge me in the opportunity which this chapter affords of relating the facts; lest my silence should be misconstrued into an acknowledgement of the truth of what the doctor has said." (Pott, P.–*A Treatise on Ruptures,* 2d. ed., p.139.)

Then, following an explanation of the manner in which (through investigations upon foetuses and stillborn infants) he had reached his opinions concerning the *hernia congenita,* the author launches upon his defense.

The account which he gives of his visit to Dr. Hunter's dissecting room, at the time when John Hunter received him, is much the same in general as that of Dr. Hunter, but his version of the details of the discussion that took place is altogether different. Concerning this visit, Pott writes as follows:

> "Having always entertained a high opinion of Dr. Hunter's *anatomical* abilities, I called at his house designing to have told him what I had done, and to have had some conversation with him on the subject: the doctor was not at home, but his brother Mr. Hunter was, and with him I had some talk. The same gentleman also shewed me *one single preparation, tied down, in a glass, in spirit,* exhibiting the situation of the testicles of a foetus pretty near the time of their passing from the abdomen into the scrotum, of which kind I had then several at home, and which many of my friends had seen. Mr. Hunter did not show me any other preparation of any kind whatever, nor do I remember that the

congenial hernia was once mentioned by either of us during my short visit, notwithstanding the doctor has said that his brother "showed me his preparations with great readiness, and explained to me his (the doctor's) hypothesis of the contiguity of the intestine and testicle." Our conversation turned intirely on the passage of the testis from the belly into the scrotum, and as far as I could perceive (for he spake with the most cautious, apprehensive reservedness) our sentiments were alike."

My papers were at this time finished and corrected for the press; . . . ; nor did I alter a single syllable in them, in consequence of this visit to Mr. Hunter: . . . . (*ibid.*—p.145.)

* * * * *

This is a short and true account of the fact; this is the thing for which I have been traduced in print, as a plagiarist, and for which Dr. Hunter has taken a liberty with me, which he can have no right to take. (*ibid.*—p.147.)

To the charge that "Mr. P. borrowed a remarkable paragraph from Baron Haller [that in which it is said the testicle descended after birth, caused by the movements of respiration], and gave it to the world as his own in the first edition of his general Treatise on Ruptures"; (Hunter, Wm.—*A Supplement etc.*, p.6) Mr. Pott replies: "I do aver, that I never had seen, read, or heard of the book . . ., till some time after the publication of my pamphlet on that subject: I therefore did not, nor could borrow any part of the contents, either of that, or of my former treatise, from it: the manner in which I attained my knowledge [by personal investigations] I have already most faithfully related, and therefore think myself intitled to the reader's credit. But setting aside whatever pretension I may have to be believed upon my bare assertion; is it probable that if I had stolen my opinion from the baron's book, that I should have given so short, so imperfect, and indeed so erroneous an account of what he has so fully explained, or at least so clearly pointed out?" (Pott, P.—*A Treatise on Ruptures*, 2d. ed., p. 149.)

To the statement made by William Hunter that: "It was what any of my pupils might have written;" Pott retorts:

"I do indeed most sincerely wish that some one of the doctor's pupils had prevented me from being engaged in this affair, by having published what, *he says, they all knew;* to which he

might have added, *and they only;* for the rest of the medical world were so totally unacquainted with the subject, that mean and trite as my performance was, I received the thanks of many, I might say most of the practitioners of eminence, both in physick and surgery, for it. They acknowledged themselves pleased and informed, and thought that it furnished them with a new idea; and what is more, do still continue to think so, notwithstanding the doctor's assertion." (*ibid.*—p.153.)

Having spoken his mind and presented his defense, Percivall Pott concludes his remarks by "closing the door" to further part in this controversy, by writing as follows:*

"As I did neither *wantonly seek* this dispute, nor begin it, so now having said all that I know, or think concerning it, I am determined never to write another word on the subject; I therefore take my leave of it for ever, assuring both Dr. Hunter and his brother, that when I published my tract on the congenial hernia, I had no intention to anticipate either of them, or to prevent either of them from enjoying any reputation, or honour, which might arise to them from their labours on this, or any other subject, on the contrary, when I presented my first treatise to the doctor, if he had been so friendly as to have hinted to me his suspicion of my having borrowed from Haller; or to have said, that he, or his brother, was then inquiring into that part of the animal oeconomy, I would not only have given him a true answer to the former, but should most probably never have prosecuted my inquiries into the latter, as I should have thereby known that the subject was in so able hands: I wanted no reputation of that sort; but as I thought that I had accidentally hit upon a truth in which mankind were not a little interested, so I thought it my duty to publish it. If my account was erroneous, it certainly deserved correction; but that correction might have been made with civility and candor, not in the manner in which the doctor, or his *nameless* pupil attempted it; if I had then been displeased, the fault would have been mine, and no blame could have justly been laid on the corrector. The man who is offended by a civil offer of information, has more vanity than sense; but

* Pott lived up to his word, for he never again referred to this dispute; and in the third edition of *A Treatise on Ruptures,* published in 1769, Section X, *The Congenial Hernia,* contains not a single word concerning the controversy.

> he who tacitly and tamely submits to an attempt towards rendering him contemptible (by whomsoever made) does thereby become so." (*ibid.*—p.162.)

The controversy did not, however, end here, as William Hunter could not, it seems, allow Percivall Pott to have the last word. Hence we find the former writing: "I read it [Pott's defense], and found that we differ very widely in stating the facts upon which the whole dispute between us depends." (Hunter, Wm.—*A Supplement, etc.*, p.iv.) "Yet, now that I have got all the light which he has given me; when I read over both accounts, and compared them together, I am still conscious that mine is exactly true in every particular; and that in his there are such mistakes and inaccuracies, as could not be expected from a man of his understanding and abilities, whether one considers him as a surgeon, or as an author." (*ibid.*) William Hunter felt in duty bound, it seems, in "justice to the public," as he says, as well as to himself, "to clear up the matter" by proving the truth of his accusations. This he attempts to do in *A Supplement to the First Part of Medical Commentaries* (1764), which was published in the year following the appearance of Pott's defense. The treatise contains a most detailed account of the dispute, but presents no new evidence against Pott. The text merely reiterates the charges Hunter had made and attempts to refute Pott's arguments by an analysis of his statements and the furnishing of copies of affidavits from students and practitioners to substantiate his claims. The whole treatise seems to be as uncalled for as it is undignified, in its cruel denunciation of a friend and fellow practitioner on insufficient evidence. The veracity of a man of standing in the community is willfully attacked and he is openly accused of plagiarism and denounced as a prevaricator.

It is not out of place, I think, in concluding this account, to add a few remarks upon the events that led up to the dispute and to analyze the claims put forward by the contestants in this unhappy controversy.

The credit for recognizing the relationship of the testicle to the hernia sac, in the congenital type of oblique inguinal hernia, must be given to Samuel Sharp; who, as we have seen, described the anatomical findings, but failed to identify its cause as being the result of a lack of embryological development.

There is no question that Albrecht von Haller was the first to demonstrate the relationship of the congenital hernia to the descent of

the testicle, the progress of which he describes with accuracy except for the time of its occurrence. William Hunter quite fairly acknowledges all of this in *Medical Commentaries.*

It is true that there is much to be found in Percivall Pott's two treatises that might make one believe that he had read Haller's article before publishing *A Treatise on Ruptures* in the year 1756, for he adds nothing new and continues the false conception that the testicle descends after birth. Pott, however, was, even at this time, the leading surgeon of London and known for his honesty and ethical standing in the profession. We must, in consequence, I believe, accept his word that he had not known of Haller's article when preparing his treatise. Against this statement, William Hunter puts forth much wordy argument, in which, though he produces no evidence to prove that Pott had borrowed information from Haller, he, nevertheless, points out the similarity of Pott's account of the descent of the testicle and his description of the *congenial hernia,* as he called it, to that given by Haller. On this circumstantial evidence William Hunter attempts to convict his friend on the first charge of plagiarism.

The second charge, that Pott borrowed information to be used by him, from the Hunters, can be, I think, as easily disposed of. Both of Pott's treatises on the *congenial hernia* were published, as has been noted, some years before the appearance of John Hunter's article on the *hernia congenita.* However, William Hunter assumed that he had established priority on this subject for himself and his brother; because he had included some remarks on their observations, concerning the descent of the testicle and the *hernia congenita,* in his lectures during the autumn of 1756. He further claimed, that he and his brother had both discussed this matter in detail with Pott at about the same time. Pott, though he readily acknowledged the meetings, denied the detailed discussion of this matter; in fact he writes that John Hunter "spake with the most cautious apprehensive reservedness." Comparing the subject matter of Pott's treatises with that contained in John Hunter's article, one is at once impressed with the superior knowledge of the subject, as laid down by the latter, and seeks in vain throughout the former's treatise, without finding the least suspicion that its author had used information that might have been acquired from William Hunter's lectures or through the discussions Pott had had with the brothers. John Hunter, on the other hand, presents a detailed account of his

painstaking investigation, the observations he made and the conclusions he drew, in a scientific discussion which gives much information that is new and corrects statements of others that were false. All of this has stood the test of time.

From the facts presented, one suspects that, in the first place, William Hunter's claim to priority for discovery in this instance rests upon an insecure foundation and, second, his case against Pott lacks sufficient evidence of proof. If this is so, why, may we ask, did he make so public a matter of the controversy? Perhaps it was a sense of disappointment and frustration on his part, at learning of the publication of the article on *congenial hernia*, by Pott, when he and his brother were just about to conclude their extensive and painstaking inquiry into the same subject. He may have felt, it seems, that their work had been done in vain, though he should have realized that Pott's account was poorer and less extensive than theirs, where almost every statement was backed by observed facts. William Hunter, however, possessed great pride in his reputation and, as we have seen, an inordinate sense of justice, and being jealous, appears to have thought he should defend himself, especially since his old antagonist in Edinburgh, Alexander Monro *primus*, had chided him for quarreling with Pott.

In ending, it might be added that, though today such a publicly conducted controversy over a private matter would be considered vulgar and uncalled for, this was not the case during the eighteenth century in England, when such disputes, with charges and counter-charges, were commonly aired in the public press.

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